REMARKS

Status of the Claims

Claims 1, 3-9, and 11-22 are pending in the present application. Claims 2 and 10 were previously canceled. Claims 6, 14, and 18-21 are withdrawn as directed to a non-elected invention. Claims 1, 9, 18, and 19 are amended to specify that the cells are "from leukocytes isolated from a patient." Support for this amendment is found throughout the application as originally filed including on page 7. Claims 1, 6, 7, 8, 18, and 20 are amended to specify helper "T1" cells instead of helper "T" cells. Support for this amendment is found throughout the application as originally filed including on page 7. Claims 19 and 21 are amended for consistency to specify helper T1 cells throughout the claim. Claims 9, 14-17, 19, and 21 are amended to correct minor typographical errors. No new matter is added by way of this amendment. Reconsideration is respectfully requested.

Request for Rejoinder

In view of the amendments and arguments described herein, Applicants submit that withdrawn claims 6, 14, and 18-21 should be rejoined with claims 1, 3-9, and 11-22, which are presently under consideration. All of the pending claims share a special technical feature. In particular, claims 1, 3-9, and 11-22 describe helper T1 cells from leukocytes isolated from a patient, which have a non-specific anti-tumor activity, and the impartation of antigen specificity to the cells. In view of this special technical feature, the pending claims comply with the unity of invention requirement. Accordingly, rejoinder of the withdrawn claims is respectfully requested.

Claim Objections

Claims 7 and 15 are objected to because these claims depend from withdrawn claim 6 (claim 7) or withdrawn claim 14 (claim 15), *see* Office Action, page 2. Applicants respectfully traverse. As explained above, Applicants submit that the withdrawn claims should be rejoined with the examined claims since all of the claims pending in the present application share a special technical feature. In view of Applicants' request for rejoinder, Applicants believe that claims 7 and 15 properly reference claims 6 and 14. Accordingly, withdrawal of the objection is respectfully requested.

Issues Under 35 U.S.C. § 102(b)

Fujio

Claims 1, 4, and 7 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Fujio *et al.*, *Journal of Immunology*, 165:528-532, ("Fujio"), *see* Office Action, page 3. Applicants respectfully traverse.

As amended, independent claim 1 is directed to a process of preparing cells for cell therapy, comprising the steps of: inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient; and imparting antigen specificity to the helper T1 cells wherein the step of imparting antigen specificity to the helper T1 cells comprises transducing the helper T1 cells with a T cell receptor gene that recognizes a cancer-associated antigen.

Fujio does not describe all of the elements of independent claim 1. In particular, Fujio fails to describe that helper T1 cells are obtained from "leukocytes isolated from a patient", which express T cell receptor (TCR). Fujio discloses transduction experiments, which demonstrate that TCR is expressed and functional when a class 2-restricted TCR gene is introduced into TG40 cells. TG40 cells are fusion cells, which are derived from a helper T cell and a cancer cell, *see* from page 528, right column, line 2 from the bottom of Fujio, and Reference 17 of Fujio. Accordingly, the TG40 cells described in Fujio are not obtained from "leukocytes isolated from a patient", which express TCR, as described in the amended claims.

Further, Fujio does not provide any discussion about whether the transduced TG40 cell, which is obtained by introducing an MHC class 2-restricted TCR gene into the cell, is a "Th1" cell or a "Th2" cell. Fujio does not provide any immunological experimental data which show the type of immune cell and the characteristics of the transduced TG40 cells. Applicants submit that this lack of disclosure is based on the origination of the TG40 cell. As noted above, the TG40 cell originated from the fusion of a helper T cell and a cancer cell. Accordingly, it would be nonsensical to discuss whether the cell is a Thl or Th2 cell, or which cell type is more effective in the treatment of cancer. The authors of Fujio are only interested in determining whether an exogeneous TCR gene is expressed and functional within helper T cells.

Moreover, Applicants submit that the antigen OVA (egg white albumin) used in the

Fujio's experiment is a model of an exogeneous antigen protein. Accordingly, OVA is a mere antigen, not a "tumor-related antigen", as required by the instant claims.

In view of the foregoing, claims 1, 4, and 7 fail to describe the claimed invention. Fujio fails to disclose that the cells to be transduced are obtained from leukocytes isolated from a patient. Fujio does not teach that helper T1 cells were induced after transduction. Further, Fujio fails to describe a tumor-related antigen. Accordingly, Fujio does not anticipate the instant claims and withdrawal of the rejection is respectfully requested.

Kessels

Claims 1, 3, 7, 9, 11, and 15 are also rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kessels *et al.*, *Nature Immunology*, 2:957-961, ("Kessels"), *see* Office Action, pages 4-5. Applicants respectfully traverse.

Amended independent claim 1 is described above. Amended independent claim 9 is directed to a process of preparing cells for cell therapy, comprising the steps of: inducing helper T1 cells and cytotoxic T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient; and imparting antigen specificity to the helper T1 cells and cytotoxic T1 cells wherein the step of imparting antigen specificity to the helper T1 cells and cytotoxic T1 cells comprises transducing the helper T1 cells and the cytotoxic T1 cells with a T cell receptor gene that recognizes a cancer-associated antigen.

Kessels describes transducing a virus antigen-specific, class 1-restricted TCR gene into killer T cells, or into whole spleen cells containing helper T cells, *see* from page 958, left-column, line 3, and Fig. 1 of Kessels. The results show that killer T cells, specific to the virus antigen were induced, *see* Fig. 2 and Fig. 3, from page 958, left-column, line 3 of Kessels. However, no expansion of helper T cells (CD4+ T cells), which were specific to the virus antigen, were detected, *see* from page 959, left-column, line 9 of Kessels. Regarding the lack of induction of helper T1 cells, the authors suggest that cooperation of the transduced class 1-restricted TCR with CD4 antigen of the helper T cells and proper signaling toward the helper T cells did not work well, *see* from page 959, left column, line 14 of Kessels. Accordingly, Kessels teaches that helper T1 cells could not be induced.

In view of the foregoing, Kessels fails to describe inducing helper T1 cells. Accordingly, the claims are not anticipated by Kessels. Withdrawal of the rejection is respectfully requested.

Issues under 35 U.S.C. §103(a)

Fujio, Tsuji, Kessels, and Nishimura

Claims 1, 3, 7-9, 11, 12, 15-17, and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Fujio in view Tsuji *et al.*, *Cancer Science*, 2003, 94:389-393, ("Tsuji"), Kessels and Nishimura, *Cancer Treatment and Host*, 12:363-373, ("Nishimura"), *see* Office Action, pages 5-10. Applicants respectfully traverse.

According to the Examiner, Fujio disclose all of the elements of the instant claims, except for the transduction of Th1 cells with MHC class I-restricted TCR gene or the transduction of both Th1 and Tc1 cells with the TCR gene. Nevertheless, the Examiner believes that Tsuji, Kessels and Nishimura remedy these deficiencies.

Legal Standard for Obviousness

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007).

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The claims are not rendered obvious by the cited references

As noted above, the TG40 cells described in Fujio result from the fusion of a cancer cell and a helper T cell. Accordingly, Fujio does not describe whether or not the transduced cells described therein are Th1 cells or Th2 cells since such a description would be nonsensical in the context of Fujio. Nishimura merely teaches that helper T1 cells are preferable in the methods described therein due to anti-cancer effects. Nishimura further describe the necessity of using MHC class 2 associated peptides with these cells. Nevertheless, Nishimura does not teach or suggest the introduction of a TCR gene into helper cells for the induction of helper T1 cells. Further, Nishimura does not describe how to introduce helper T cells. Nishimura does describe,

however, that Th1-dominant immunity is advantageous. Nevertheless, Applicants submit that an ordinary artisan could not have conceived of the claimed invention from the combination of Fujio and Nishimura. That is, this combination of references would not teach or suggest to an ordinary artisan the induction of helper T1 cells obtained from leukocytes isolated from a patient and the introduction of a MHC class 1-restricted TCR gene into the helper T1 cells as described in the pending claims.

Applicants submit that the TG40 cells of Fujio and the helper T cells that are isolated from a patient, as described in the instant claims, are completely different in nature. Further, the expression of an exogeneous TCR gene within the TG40 cells in comparison to the claimed method, which concerns the introduction of class 1-restricted TCR gene into helper T cells isolated from a patient, are completely different methods, which utilize different cell mechanisms and functions. Accordingly, an ordinary artisan could not have reasonably predicted that replacing the TG40 cells of Fujio with helper T1 cells derived from leukocytes isolated from a patient and introducing MHC class 1-restricted TCR gene into helper T cells would have resulted in the induction of antigen specific helper T cells.

Kessels fails to remedy the deficiencies of Fujio and Nishimura. In fact, Kessels teaches away from the claimed invention. As noted above, Kessels' results show that expansion of helper T cells, specific to a virus antigen was not detected. Based upon the disclosure of Kessels, an ordinary artisan would have expected that, even if a class 1-restricted TCR gene is introduced into helper T cells (a cell population containing helper T cells), antigen specific helper T1 cells would not be induced. As noted above, regarding the lack of induction of helper T1 cells, the authors suggest that cooperation of the transduced class 1-restricted TCR with the CD4 antigen of the helper T cells and a proper signaling toward the helper T cells does not work well, *see* from page 959, left-column, line 14.

Contrary to the report of Kessels, the present invention demonstrates that both the introduced class 1-restricted TCR and the CD4 antigen of the helper T1 cells are functional. It is not clear what type of experimental conditions or manipulation contributed to the inconsistency of the present invention and Kessels' results, but as noted above, Kessels, indeed, reports that "helper T1 cells could not be induced."

Tsuji fails to remedy the deficiencies of Fujio, Nishimura and Kessels. Tsuji discloses that a class 1-restricted TCR gene is introduced into killer T cells, *see* Tsuji, from page 389,

right-column, line 3 from the bottom, to induce functional killer T cells, *see also* Figs. 3 and 4 of Tsuji. Applicants note that killer T cells have completely different properties and functions from helper T cells. For example, a killer T cell is a CD8-positive T cell and a helper T cell is a CD4-positive T cell. Accordingly, any findings obtained from transduction experiments using killer T cells would not have allowed an ordinary artisan to reasonably predict that functional helper T1 cells could have been prepared by transducing helper T cells with a TCR gene.

In view of the foregoing, Applicants submit that the disclosure of Tsujii regarding killer T cells is totally unrelated to the present invention. Accordingly, Applicants believe that Tsujii is not relevant to the present invention.

For the reasons set forth above, an ordinary artisan would not have reasonably expected to achieve the instant invention from the cited reference combination. Applicants further submit that an ordinary artisan could not have conceived of inducing antigen specific helper T1 cells by introducing class 1-restricted TCR gene into TG40 cells as disclosed in Fujio. Applicants also submit that an ordinary artisan would not have even conceived of inducing antigen specific helper T cells according to the claimed method from the combination of references. Moreover, Kessels reports that, when a class 1-restricted TCR was introduced into spleen cells containing intact helper T cells, antigen specific helper T cells could NOT be induced. This teaching away also support Applicants submission that an ordinary artisan could not reasonably expected to achieve the claimed method from the cited references. Accordingly, withdrawal of the rejection is respectfully requested.

Fujio and Gaiger

Claims 1 and 5 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Fujio in view of U.S. Patent No. 7,323,181 to Gaiger *et al.*, ("Gaiger"), *see* Office Action, pages 10-11. Applicants respectfully traverse.

The Examiner states that Fujio describes all of the elements of the instant claims except for the cancer-associated antigen, Wilms' Tumor 1, ("WT1"). Nevertheless, the Examiner states that Gaiger teaches this element.

As noted above, Fujio fails to describe all of the elements of the instant claims. In particular, Fujio fails to describe that the cells to be transduced are obtained from leukocytes isolated from a patient. Fujio also does not teach that helper T1 cells were induced after

transduction. Applicants submit that the teachings in Gaiger fail to remedy these deficiencies. Gaiger is merely cited for introducing genes encoding T-cell receptor chains for WT1 to improve the response to WT1 bearing leukemia and cancer cells, *see* Office Action, page 11.

In view of the foregoing, claims 1 and 5 are not rendered obvious by the combination of Fujio and Gaiger. Withdrawal of the rejection is respectfully requested.

Kessels and Gaiger

Claims 9 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable Kessels in view of Gaiger, *see* Office Action pages 12-14. Applicants respectfully traverse.

As noted above, Kessels fails to describe inducing helper T1 cells. Kessels also teaches away from the instant invention. Gaiger does not remedy these deficiencies and is merely cited for describing WT1. Accordingly, claims 9 and 13 are not rendered obvious by the combination of Kessels and Gaiger. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendment and remarks, Applicants believe the instant application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Ph.D., Registration No. 46,046, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

By _____

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